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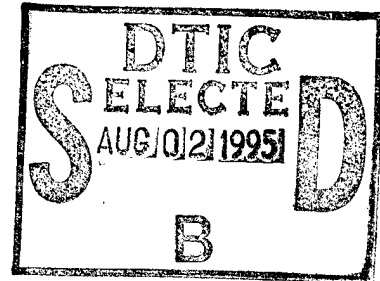
TITLE: Predoctoral Training Program in Breast Cancer Research

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FOREWORD

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TABLE OF CONTENTS

	Page
Front Cover	
Report Documentation Page	2
Foreword	3
Table of Contents	4
Introduction	5
Progress	5
Conclusions	7
References	7
Appendix	7

INTRODUCTION

This training grant for 5 predoctoral students was designed to integrate students in diverse disciplines with a common interest in understanding breast cancer. The special features of this training grant was proposed to be a journal club designed to facilitate the exchange and discussion of current literature and research in breast cancer, the initiation of a yearly retreat to encourage interactions between breast cancer training grant participants, and the initiation of a special seminar series involving a guest speaker prominent in the field of breast cancer research.

PROGRESS

Students:

The following five students were supported by the Breast Cancer Training grant between June 1, 1994 to May 31, 1995. Listed is the accomplishments in the form of publications or abstracts for each student during this time.

Mark Alexandrow. Third/fourth year student, laboratory of Harold L. Moses, Dept. of Cell Biology. Progress on this grant is demonstrated by the following abstract, review article, and submitted manuscript.

Alexandrow, M.G. and H.L. Moses, "Late-G1 effects of c-myc on TGF β 1-induced inhibition of mouse keratinocytes". presented at Keystone Symposium "Oncogenes: 20 years later", Jan, 1995.

Alexandrow, M.G., and H.L. Moses "Transforming growth factor β and cell cycle regulation". Cancer Res. 55: 1452-1457, 1995

Alexandrow, M.G., and Moses, H.L. "TGF β 1 inhibits mouse keratinocytes late in G1 independent of effects on gene transcription" submitted

Renee Bailey. Second/third year student, laboratory of Fritz Parl, Dept. of Pathology. Progress on this grant is demonstrated by an abstract submitted to The Endocrine Society entitled

Bailey, L.R., Yee, C.J., Verrier, C.S., Roodi, N., and Parl, F.F., "Estrogen induction of WAF1/Cip1 in MCF-7 breast cancer cells by a p53-independent pathway".

Mike Engel. MSTP student, First/second year of graduate training, laboratory of Harold L. Moses, Dept. of Cell Biology. Research progress during this grant period is summarized in the following paragraphs.

Considerable effort was directed toward identifying signal transducing proteins in the TGF- β receptor signaling pathway. Two candidate proteins were detected by a yeast interaction-trap screening of a Hela cell library with the cytoplasmic domain of the type I

TGF- β receptor (Alk-5). The first protein, known as FKBP12, is a member of the immunophilin class of cytoplasmic proteins and derives its name from its ability to coordinate the interaction between the immunosuppressive agent FK-506 and its target phosphatase, calcineurin. Based upon the data from the yeast two-hybrid screen and supportive data from an in vitro binding assay, it was hypothesized that FKBP12 might play a role in transduction of growth inhibitory or immunosuppressive signals by TGF- β . However, the interaction was not detectable in vivo.

The second candidate protein identified in the interaction trap screen was the α -subunit of the heterodimeric enzyme farnesyl transferase. This enzyme plays an essential role in the isoprenylation of various substrates, including p21-ras, nuclear lamins A and C, and the γ -subunits of heterotrimeric G- proteins. The potential role of this enzyme in TGF- β mediated signal transduction both in vitro and in vivo was explored. While in vitro data with regard to this relationship is promising, an in vivo relationship of either an interactive or functional nature has not been demonstrated.

Recently, issues related to the specificity of signal transduction by the TGF- β receptor and other members of this receptor family such as the activin and BMP receptor complexes has been investigated. It is of interest to know to what degree disruption of one signaling pathway, for example by the introduction of dominant negative constructs, interferes with signal transduction by other receptor family members. Furthermore, the inducible transcription systems can be used to quantitatively assess receptor "cross talk" if it exists.

Laura J. Niedernhofer, MSTP student, second/third year of graduate training, laboratory of Larry Marnett, Dept. of Biochemistry.

Progress on this grant is summarized by an abstract presented at the Eighth International Conference on Carcinogenesis and Risk Assessment.

Niedernhofer, L.J., Chaudhary, A.J., and Marnett, L.J. "Mutagenicity of Malondialdehyde in Human Cells".

Cindy J. Yee. Second/third year student, laboratory of Fritz Parl, Dept. of Pathology. Progress on this grant is demonstrated by two manuscripts and an abstract.

C.J. Yee, N. Roodi, C.S. Verrier, and F.F. Parl. "Microsatellite instability and loss of heterozygosity in breast cancer". Cancer Res. 54: 1641-1644, 1994.

N. Roodi, L.R. Bailey, W-Y Kao, C.S. Verrier, C.J. Yee, W.D. Dupont, and F.F. Parl. "Estrogen receptor analysis in estrogen receptor-positive and receptor-negative primary breast cancer". J. N.C.I. 87: 446-451, 1995.

C.J. Yee, C.S. Verrier, L.R. Bailey, N. Roodi, and F.F. Parl, "Molecular characterization of lobular breast cancer". abstract presented at the 86th Annual Meeting of the American Association for Cancer Research, Toronto, Canada

Journal Club

The Breast Cancer Training Grant met monthly in the Vanderbilt Cancer Center Conference Room. The original plan to meet bimonthly was altered to a monthly meeting in view of the active seminar series supported by the Vanderbilt Cancer Center which meets on a weekly basis. Each student presented either a research seminar on their own work, or a topic of current interest to the group. Laura Rudolph, a predoctoral student supported by an individual training grant for the Dept. of the Army Breast Cancer Research Initiative also participated in this journal club. In addition, a faculty member and an outside speaker were invited to present their research during this time.

Retreat

The retreat for the Breast Cancer Training Program is held in conjunction with the retreat for the Breast Cancer Program for the Vanderbilt Cancer Center. In 1994 this retreat was held on the Vanderbilt campus in June and there was insufficient time to include the Breast Cancer Training Grant participants. In 1995 the retreat will be held September 9 at Montgomery Bell State Park and all Breast Cancer Training Grant grantees are expected to attend and present a poster. For the 1994 year, we supported the travel of two trainees to attend the annual meeting of the American Association of Cancer Research and the Endocrine Society meeting to present posters.

Seminar speaker

The Breast Cancer Training Grant supported the visit of Dr. Bill Muller, McMaster University, on May 25, 1995. Dr. Muller presented an excellent seminar on his recent work using a transgenic mouse system to study signal transduction in mammary carcinogenesis. The Breast Cancer Training Grant students met with Dr. Muller over lunch following the seminar. There was considerable interest and excitement over the work presented and this proved to be a very valuable training opportunity for the students.

CONCLUSIONS

The Breast Cancer Training Grant has been implemented and has supported 5 excellent students for the past year. Four abstracts, 3 publications, and a submitted manuscript with relevance to breast cancer resulted from this support. The monthly journal clubs proved to be excellent opportunities to become acquainted with the breast cancer-related work performed by members of the group as well as in the literature. The opportunity to meet the visiting seminar speaker was judged a valuable experience. The Breast Cancer Program retreat was not accomplished this past funding period but is planned for September, 1995.

REFERENCES - Not Applicable

APPENDIX - Not Applicable